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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,587	10/23/2006	Shinichi Hirose	2006_1477A	3395

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
08/23/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/591,587	HIROSE ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2010*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *5 and 6* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *5 & 6* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on *10/07/2010*has been entered.

Applicant's response filed on *10/07/2010* in response to office action mailed on 03/04/2010 has been acknowledged.

Claims 1-4 canceled.

Claims 5 & 6 are pending and are examined in this office action

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.*** *The Affidavit filed by Dr. Tatsuya Tanaka on behalf of the instant invention is fully considered for this Office Action.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5 and 6 stand rejected under 35 USC 103 (a) as being unpatentable over Matsuhima et al (2002, Epilepsy Research 48:181-186; art of record) and in view of McColl et al (2003, Neuropharmacology 44:234-243).

The above claims are drawn to a transgenic rat that comprises in its genome a mutant CHRNA transgene encoding the polypeptide of SEQ ID NO:3 with the mutation S286L and said transgene is operably linked to a promoter and expressed in brain of the transgenic rat said transgenic animal develops a phenotype of spontaneous epileptic seizures during sleep. In further limitations said transgene is fused to a promoter of a gene that is specifically expressed in cerebrum cortex and hippocampus. In still further limitations said transgenic animal is a rat having the nucleotide SEQ ID NO:2 which carries nucleotide base changes at position 865 from C to T and at position 866 from T to C.

Regarding above claims Matsuhima clearly teaches that the electrophysiological characteristics of an acetylcholine receptor with a rat chrna4 mutant with a mutation corresponding to human Ser284Leu of CHRNA4 and reconstituted in xenopus oocytes produced a receptor with changed electrophysiological properties (entire article, abstract). This suggested that a mutation in amino acid corresponding Ser284 of CHRNA4 in non-human animal systems lead to reduced acetylcholine receptor activity similar to that is found in alpha4-subunit mutation harboring of ADFNLE patients (entire article; abstract; p.182 col.1-2; p.184 col.2 bridging p.185). Regarding the difference in the mutant amino acid position in CHRNA polypeptide of rat (SEQ ID NO:3) as compared to that of humans (CHRNA S284) the prior art clearly teaches several sequence alignment methodologies

(e.g. Clustal-W sequence alignment program) that one of skill would use to figure out the corresponding amino acid or nucleotide positions in the orthologs and in other phylogenetically related genes. Matsuhima also clearly teaches that the corresponding location (position#) of the amino acid S284 of human CHRNA4 may vary in CHRNA4 of different animals (p.182 col.1, 3rd paragraph; p.184, col.2) and further teaches that said mutant CHRNA transgene reduces acetyl choline receptors similar to other mutations in the alpha4 subunit found in atuosomal dominant NFLE (entire article; abstract; p.182 col.1; p.184, col.2) i.e., by dominant negative effect on the receptor function and further envisions that experimental animal models bearing mutations in CHRNA4 would be a good model for ADNFLE (p.185, col.1, 3rd paragraph). Matsuhima however does not teach making a transgenic animals or rat with a mutant CHRNA transgene.

McColl teaches developing transgenic mice that are transgenic or knockout with respect to CHRNA4 mutations that are associated with ADNFLE (entire article, abstract). McColl further teaches that an in vitro mutant CHRNA4 functional studies with the alpha-4 polypeptide mutations for example S252L and S284L (that corresponds to rat S286L) suggest receptor hypofunction and further teaches making mouse carrying mutations or deletions in CHRNA4 that results in hypo-function of the receptors and exhibiting certain phenotypes of ADNFLE (entire article, abstract).

Further regarding dependent claim limitation of mutating the specific nucleotides of the codon (at position 865 from C to T and at position 866 from T to C) so as to encode said mutated amino acid, one of skill in the art is well aware of the sequences required for

encoding the amino acids, and hence, the specific mutations in the encoding sequence are obvious.

Thus it would have been obvious for one of ordinary skill in the art to generate a transgenic rat by introducing a mutant CHRNA transgene corresponding mutation (e.g., S284L of humans or S286L of rats) that cause epilepsy (ADFNLE) in humans as taught by Matsuhima and develop an animal model with ADNFLE phenotype because of receptor hypofunction as taught by McColl with transgenic mice.. One of ordinary skill in the art would have been motivated to make and use a transgenic mouse or a rat with a corresponding human disease causing mutation, as it would provide an appropriate model system for drug screening and experimental therapy of ADNFLE. One of skill in the art would have a reasonable expectation of success making using a transgenic mutant animal with a mutation corresponding to human S284L or rat S286L because the prior art clearly teaches that this would result in hypofunction of nicotinic AChRs and would lead to a ADNFLE phenotype and the art further amply teaches the general methodologies for generating transgenic mice and rats. Thus, the claimed invention was *prima facie* obvious.

Response to Applicants Arguments of 10/07/2010:

Applicants' arguments of *10/07/2011* and the Affidavit filed by Dr. Tatsuya Tanaka on behalf of the instant invention is fully considered for this Office Action. Affidavit filed by Dr. Tatsuya Tanaka clearly highlights that there currently exist at least 9 different animal models for ADNFLE and all of them however belong to mouse species. Instant

invention however, is based on a Rat species. Both mouse and rat however belong to a sub group of closely related animal species called Rodentia. The mutant transgenes used and the methodology used in generating these animal model is similar and the mutant genes were previously established as causing abnormality related to ADNFLE in humans. However, according to Dr. Tatsuya Tanaka, the transgenic rat of the instant invention, unlike the mouse models cited, more closely reflects human ADNFLE condition called "nocturnal paroxysmal arousal" or the spontaneous epileptic seizures during sleep. Dr. Dr. Tatsuya Tanaka claims it as an "unexpected" phenotype.

The arguments are however found not fully persuasive because there seems to be variability in the highlighted ADNFLE phenotypes in the different animal models in the cited prior art and are within the broad spectrum of ADNFLE phenotypes in humans. Since the mutant genes and the general methodology used in generating these different animal models including the transgenic rat of instant invention is same or similar except for the species difference, it is not clear why the instant invention be regarded as "unexpected result'. Applicant has not highlighted either in claims or the specification why this could be. Is it due to a specific promoter used for expressing the transgene? Applicant only broadly claims using a "promoter" that is "expressed" in the brain (being non-specific to any part of the brain). Or is it due to difference in genetic back ground? Only difference highlighted is the species difference (mouse Vs. rat). In the absence of clear description in the specification regarding why this invention be considered "unexpected result", given the common methodology and the known mutant genes used in the generation of instant "transgenic rats", the invention is clearly

would have been obvious to the artisan at the time of invention. The Applicant further should note that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art. .Hence the obviousness rejection as promulgated above is maintained.

Conclusion

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.,* may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private

PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/ROBERT M KELLY/

Primary Examiner, Art Unit 1633